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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER	
			PALENIK, JEFFREY T	
		ART UNIT	PAPER NUMBER	
		1615		
		NOTIFICATION DATE	DELIVERY MODE	
		09/15/2009	ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/551,901	<b>Applicant(s)</b> MIURA ET AL.
	<b>Examiner</b> Jeffrey T. Palenik	<b>Art Unit</b> 1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 29 June 2009.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-4,7 and 10-23 is/are pending in the application.  
 4a) Of the above claim(s) 14-23 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-4,7 and 10-13 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/1450B)  
 Paper No(s)/Mail Date \_\_\_\_\_
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_  
 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

**STATUS OF THE APPLICATION**

Applicants' amendments and remarks, filed 29 June 2009 regarding Application N° 10/551,901, are acknowledged and entered on the record. The Examiner acknowledges the following:

Claims 1-4, 7, 10-23 are pending, where claims 14-23 remain withdrawn from consideration.

Claims 5, 6, 8 and 9 are newly cancelled.

Of the remaining claims under consideration, it appears that claim 1 has been amended to incorporate the property limitations of cancelled claims 5, 6 and 9.

No new claims have been added.

The Examiner acknowledges that no new matter has been added to the claims.

Thus, claims 1-4, 7 and 10-13 now represent all claims currently under consideration.

**INFORMATION DISCLOSURE STATEMENT**

No new Information Disclosure Statements (IDS) have been filed for consideration.

**WITHDRAWN OBJECTION**

**Objection to the Specification**

Applicants' remarks with regards to the objection raised under 35 U.S.C. 132(a) for introducing new matter into the specification have been reconsidered and are persuasive. Further

review reveals that the issue is not one of new matter, rather it is one of priority. The objection stands **withdrawn**.

#### PRIORITY

The present application is a national stage entry of PCT/JP04/06141 (WO 2004/096280) which was originally filed 28 April 2004. PCT/JP04/06141 further claims priority from US Provisional Application N° 60/466,069 filed 29 April 2003. The present application has on file, two Specifications: one filed 4 October 2005 and another filed 18 July 2008. The latter is attested to by Applicants as being an English-language translation of the provisional application. The Examiner understands this to be a translation of the documents filed with 60/466,069. However, there are discrepancies between the two specifications presently on file. The changed material includes: **removal** of Examples 7 and 8, as well as Comparative Examples 3 and 4 from Table 1 (page 22 of either Specification) and associated text thereto (pp. 18-21; Spec. filed 4 Oct. 2005). Applicant has also amended the disclosure **adding** the following sections: (1) Production Example 2, and (2) Industrial Applicability. Based on a comparison of the different Tables, it appears that the specification filed on 18 July 2008 is consistent with the PCT application, whereas the specification filed on 4 October 2005 is consistent with the '069 provisional application. Given that the information does not appear to be consistent between the PCT and the provisional application to which it claims priority, the Examiner at this time denies Applicants priority to said provisional application. Since the PCT application sets forth subject matter not discussed in the provisional application, Applicants are only entitled to an earliest effective U.S. filing date in accordance with the PCT application which is determined to be 28

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April 2004.

#### **MAINTAINED REJECTIONS**

The following rejection is maintained from the previous Office Correspondence dated 28 November 2008 since the art which was previously cited continues to read on the claims as presently amended.

#### **CLAIM REJECTIONS - 35 USC § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Verhoff et al. (US Pre-Grant Publication N° 2002/0047058).

The instantly amended claims are now directed to a composition comprising a very low water-soluble drug and a porous material, wherein said drug has a solubility of less than 10 µg/mL at 25°C prior to treatment and said porous material is not a porous silica material having the recited properties (claim 1 and 5-10). The limitation whereby said composition is “produced by treating a mixture ... with a supercritical or subcritical carbon dioxide fluid” is still interpreted by the Examiner as a product-by-process limitation which holds no patentable weight (MPEP §2113), particularly in absence of evidence to the criticality of the limitation. With regard to the limitations recited in claim 1, which states that said drug “has a solubility of less

than 10 µg/mL at 25°C prior to treatment”; until some material difference in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward “a very low water-soluble drug” (i.e. a water-insoluble or poorly-soluble drug), which is instantly claimed. The porous material, as discussed above, is further limited to recited embodiments which fall outside of the scope of the porous silica material parameters excluded in claim 1. Limitations to the porous material, such as silicon dioxide, are further recited (claims 2-4). With regard to the limitations recited in claims 5-10, which state limitations to the porous material such as “wherein the porous material has an average pore diameter of...” or “wherein the porous material has a specific surface area of ...”; until some material differences in the properties of the porous material of the composition or in the composition itself are demonstrated, said limitations are considered by the Examiner to be directed towards the instantly claimed composition. Claim 13 recites a drug composition comprising the composition of the instant claim 1 (i.e. a composition comprising a poorly soluble drug and a porous material).

Verhoff et al. teach the preparation of a drug product (e.g. composition) comprising a commixture small particles of a solid substrate and small particles of a first material, the combination of which is treated (e.g. milled) in the presence of a fluid carrier (claim 1). Said solid substrate is further taught as either a poorly water-soluble or water-insoluble pharmaceutical agent (claims 5 and 6). The small particles of first material are further taught as consisting of silicon dioxide (claim 17). Verhoff expressly teaches using drugs which are insoluble in water. The term “insoluble” is interpreted by the Examiner as teaching zero solubility in water, which is less than the recited property limitation of the instantly claimed

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drug. Regarding the exclusionary properties of the silica material recited in the instant claim 1, as well as the parameters of claims 2 and 3, the teaching of silicon dioxide in claim 17 as the “first material” expressly anticipates these properties. Furthermore, the “fluid carrier” of claim 1, is further taught in ¶[0149] as comprising a single component or mixture or solution of one or more subcritical or supercritical fluid such as supercritical carbon dioxide. Given these teachings, it further follows that the drug product of the instant claim 13 is also clearly anticipated.

#### **CLAIM REJECTIONS - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verhoff et al. (US Pre-Grant Publication N° 2002/0047058) in view of Yanaki et al. (USPN 5,538,728).

The instantly amended claims are directed to a composition comprising a very low water-soluble drug and a porous material and a drug product thereto, as discussed above. Claim 11 further limits the composition by reciting a weight ratio of the drug to the porous material ranging from 0.1:1 to 1:1,000. Claim 12 recites that the drug is either 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one or prednisolone valerate acetate.

The teachings of Verhoff et al. are discussed above. Verhoff further teaches that the poorly-soluble/water-insoluble active agent may comprise drug classes such as anti-inflammatory agents and steroid hormonal agents such as prednisolone and prednisone ¶[0256] and [0257]. Preferred milling media compositions are taught as comprising adjustable concentrations of the solid substrate, fluid carrier and milling media bodies of a first material depending upon the application ¶[0247]. For example, the ratio of the first material (e.g. silicon dioxide) to a second material is taught as ranging as broadly from 1:1000 to 1000:1.

Verhoff fails to expressly teach Applicants' claimed ratio range of drug to porous material, recited in claim 11, as well as either of Applicants' claimed drug species, recited in claim 12. However, it is known in the art that compositions comprising porous silicate materials

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such as silicon dioxide may be prepared further complexing with it poorly soluble active pharmaceutical agents are taught as evidenced by Yanaki et al.

Yanaki et al. teach a pharmaceutical composition comprising a complexation of a water-swellable silicate mineral and a drug (claims 12 and 1). Said water-swellable silicate material is taught as including silicon dioxide (col. 4, lines 15-20). The pharmaceutical used in the invention while not particularly limited, is generally taught as including a steroid hormone such as prednisolone valerate acetate, for instance where the application applies to rectal administration (col. 10, lines 40-45).

Similar to Verhoff, Yanaki fails to expressly teach Applicants' claimed drug/porous material ratio ranging as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a composition comprising the combination of a poorly water-soluble drug and a porous silica material as taught by Verhoff and suggested by the combination of Verhoff and Yanaki, modify the ratio of drug to porous material, and produce the instantly claimed composition.

One of ordinary skill in the art would have been motivated to do this because Verhoff expressly teaches the instantly claimed porous silicon dioxide/drug composition, including preparing said composition by milling in the presence of a fluid carrier such as supercritical carbon dioxide. Though Verhoff does not expressly teach incorporating prednisolone valerate acetate as the poorly water-soluble active ingredient complexed in the preparation, the motivation to do so is provided by the fact that Verhoff does teach using the less-derivatized

steroidal anti-inflammatory prednisolone as the insoluble solid substrate ¶[0257]. Coupled with the guidance of the invention to Yanaki, the skilled artisan would be well motivated to substitute prednisolone valerate acetate for prednisolone in the invention to Verhoff and produce the instant invention.

The combined references do not expressly teach the ratio limitations of poorly-soluble drug to porous material, as instantly claimed by Applicants. Since the values of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. In the instant case, the skilled artisan, would be highly motivated to adjust the aforementioned ratio in view of the teachings presented by Verhoff where it is discussed that the concentrations of the components in the preparation (i.e. the first material, the solid substrate and the milling media) can be optimized based on such requirements as milling performance and flow characteristics of the substrate to be milled ¶[0247]. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

#### **RESPONSE TO ARGUMENTS**

Applicants' arguments with regard to the rejection of claims 1-4, 7 and 13 under 35 USC 102(b) as being anticipated by Verhoff et al., as well as the rejection of claims 1-4, 7 and 10-13 under 35 USC 103(a) as being unpatentable over the combined teachings of Verhoff and Yanaki et al., have both been fully considered, but neither are persuasive.

Applicants argue on behalf of both rejections that the Verhoff reference neither anticipates nor renders obvious the instantly amended base claim. As discussed above, Applicants have amended said base claim with the properties of cancelled claims 5, 6 (pore diameter) and 9 (specific surface area). The crux of Applicants' assertion is that the Nyacol 9950 (e.g. one of the preferred silica components which is used in the invention practiced by Verhoff), has a specific surface area of 80 m<sup>2</sup>/g, which falls outside of the amended range of 100-1,800 m<sup>2</sup>/g. Applicants' have provided a product data sheet for the Nyacol 9950 (e.g. Bindzil 9950) which supports this data. Applicants have also submitted a Declaration under 37 CFR §1.132 in order to demonstrate the difference in dissolution between those compounds in the art versus those which are instantly claimed. On these grounds, Applicants allege that Verhoff fails to teach employing a porous material as recited in claim 1.

In response, the Examiner respectfully disagrees and submits that despite expressly teaching the use of Nyacol 9950 (see ¶[0108] and Examples 1-3), it is not the only silica compound which is preferably taught by Verhoff. Rather ¶[0108] teaches other silica components which do meet the specific surface area limitations, such as NALCO® 2326. The trademarked silica compound known and defined in the art as NALCO® 2326 and is also known

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to have a specific surface area property value of 600 m<sup>2</sup>/g (see ¶[0069] of US Pre-Grant Publication N° 2003/0220204).

Regarding the additional preferred silica teachings of Verhoff, MPEP §2123 (I), states that “[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including non-preferred embodiments”. Regarding said embodiments, it is further stated that “[d]isclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiment” (MPEP §2123 (II)). Thus, on these grounds, the Verhoff reference is considered by the Examiner as continuing to anticipate the instantly amended invention.

#### **RESPONSE TO DECLARATION**

Applicants' Declaration, filed 29 June 2009, under 37 CFR §1.132, has been fully considered by the Examiner but is not persuasive. The experimentation carried out by Applicants appears to consist of a Dissolution Test which contrasts the percent dissolution of a drug from a system which uses a porous silica material (Example 1) and a non-porous silica material (Example 2). Regarding the silica materials which are used in the Declaration Examples, Applicants point out that the silica materials do not meet the limitations of the average pore diameter and the specific surface area as recited by the instant claim 1. The two formulations derived within the Declaration are evaluated and observed for how much drug is released over time as a result of the ascribed dissolution method. The results of these two examples are contrasted against Examples of Table 1 in the disclosure (see pg. 22).

The Declaration is not persuasive because it is not clear what Applicants are employing in the two formulations of the Declaration Examples. Applicants never specify the “very low water-soluble drug” used in either of the Declaration Examples, whereas the formulations of Table I are limited to one of two drugs. However, given that Applicants’ specification puts no particular limitation on the type of the very low water-soluble drug is employed in the present application, the scope of the Declaration is rendered unclear.

Similarly, neither of the silica materials employed in the formulations of the Declaration are specified, except by their properties (e.g. porous/non-porous, pore diameter, and specific surface area). The properties of the silica materials appear to be what Applicants are claiming as contributing to the novelty of the composition. However, where the Declaration evaluates the dissolution on the basis of these “critical” properties, Table I in the specification does not. The criterion on which Applicants are relying and which does not appear in the Table of the Specification is the specific surface area of the silica.

Thus, given the lack of specificity in the Declaration, it is difficult to reconcile whether or not the evidence presented by Applicants falls within the scope of the instantly claimed invention.

Thus, for these reasons, Applicants’ arguments are found unpersuasive. The above rejections are hereby **maintained**.

All claims under consideration remain rejected; no claims are allowed.

#### **CONCLUSION**

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

#### **CORRESPONDENCE**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

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supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/  
Examiner, Art Unit 1615

/MP WOODWARD/  
Supervisory Patent Examiner, Art Unit 1615